DEPARTMENT OF HEALTH & HUMAN SERVICE

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 12-141/S-084
NDA 12- 142/S-102

Bristol-Myers Squibb Company
P.O. Box 4000
. Princeton, NJ 08543-4000

MAY 2 8 1999

Attention: Joseph A. Linkewich, Pharm.D.
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Dear Dr. Linkewich:

Please refer to your supplemental new drug applications dated August 25, 1998, received August 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytoxan ® Tablets (cyclophosphamide tablets, USP) and Lyophilized Cytoxan ® (cyclophosphamide for injection, USP).

We note that these supplements were submitted as a "Special Supplement - Changes Being Effected" under 21 CFR 3 14.70(c).

These supplemental new drug applications with combined package insert provide for:

1. Deletion of the statement "CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION" and insertion of "Rx only" statement.

2. The words "for injection" appearing after CYTOXAN have been deleted. The words "for injection" remain after cyclophosphamide. This change occurs throughout the package insert. The submission states that it also occurs in all labeling components (carton and labels.) Only the FPL package insert has been submitted in these supplements.

3. In the **WARNINGS** section, **Other** subsection, both sentences have been revised to read as follows: "Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported."

4. In the **ADVERSE REACTIONS** section, Respiratory System subsection, a new first sentence has been added: "Interstitial pneumonitis has been reported as part of the postmarketing experience."

5. In the **ADVERSE REACTIONS** section, Other subsection, both first sentences have been revised to read as follows: "Anaphylactic reactions have been reported; death has also been reported in association with this event.Possible cross-sensitivity with other alkylating agents has been reported." A new fourth sentence has been added: "Malaise and asthenia have been reported as part of the postmarketing experience."

6. In the References section, #7 has been revised to cite an updated reference: Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). Am J Health-Syst Pharm 1996; 53: 1669-l685.

7. The ® symbol has been added following CYTOXAN throughout labeling.

Your submissions stated November 1998 as the implementation date for the changes.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the August 25, 1999 final printed labeling. Accordingly, the supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Leslie Vaccari, Project Manager, at (301) 594-5784.

Sincerely,

Robert L. Justice, M.D. 5/28/99

Robert L. Justice, M.D.
Acting Division Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research